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(54) Title: METHOD OF INDUCING PROLIFERATION OF RETINAL STEM CELLS

(57) Abstract: The present invention relates to a method for promoting the proliferation of retinal stem cells using IL-17B. IL-17B is put into a cell culture medium containing retinal stem cells to promote the proliferation and/or differentiation of retinal stem cells. The retinal stem cells can then be transplanted into the retina to promote the growth of the photoreceptor cells, the rods and the cones. Also IL-17B can be administered directly into the retina to promote the proliferation and/or differentiation of the retinal stem cells.

5      METHOD OF INDUCING PROLIFERATION OF RETINAL STEM CELLS

BACKGROUND OF THE INVENTION

Vision is one of the most important special senses in humans. Light enters the eye and impinges on photoreceptors of a specialized epithelium, the retina.

10    The photoreceptors include rods and cones. Rods have low thresholds for detecting light and operate best under conditions of reduced lighting (scotopic vision). However, rods neither provide well-defined visual images nor contribute to color vision. Cones, by contrast, are not as sensitive as rods to light and so operate best under daylight conditions (photopic vision). Cones are responsible for high visual acuity and color

15    vision.

Information processing within the retina is performed by retinal interneurons, and the output signals are carried to the brain by the axons of retinal ganglion cells. Fetal and adult retinal stem cells give rise to all the various cell types in the retina including a) the rod and the cone photoreceptors, b) the horizontal, bipolar,

20    and amacrine interneurons, c) the ganglion projection neurons, and d) the Muller glia cells.

Degenerative diseases of the retina often result in blindness due to the destruction of the rods or cones. Retinal stem cell therapy has been developed in which retinal stem cells are harvested from the patient grown and expanded in culture and

25    reintroduced into the retina in an attempt to promote regeneration of the rods and cones. Growth factors that have been used in culture to promote proliferation of the retinal stem cells include a) transforming growth factor alpha (TGF- $\alpha$ ) and epidermal growth factor (EGF), b) fibroblast growth factor (FGF), c) TGF- $\beta$  2 & 3, and d) sonic hedgehog (shh). While these growth factors are useful, there is still a need to discover additional

30    agents to promote the proliferation and differentiation of retinal stem cells into photoreceptor rods or cones.

## DESCRIPTION OF THE INVENTION

The present invention fills this need by providing for a method of promoting the proliferation of retinal stem cells comprising bringing IL-17B into contact with retinal stem cells. Retinal stem cells can be grown in culture into which IL-17B is added and re-implanted into a patient's retina to produce functioning rods and cones of the retina. Alternatively, the IL-17B can be administered directly into retina.

The teachings of all of the references cited in the present specification are incorporated in their entirety herein by reference.

### Definitions

The term "effective amount" as used herein regarding the effective amount of IL-17B administered in accordance with the present invention means an amount of IL-17B that causes proliferation of retinal stem cells. The effective amount of IL-17B or IL-17 to be administered is from 0.1 µg to 100 µg of IL-17B or IL-17 per kilogram of body weight per day. More preferably, the effective amount is from 1 µg to 500 µg of IL-17B or IL-17 per kilogram of body weight. IL-17B should be administered daily until the symptoms of neuropathy dissipate. If the retinal stem cells are grown in culture, the concentration of IL-17B in the culture medium should be at least 100 ng/ml.

IL-17B (formerly called 'Zcyto7') and a method for making IL-17B polypeptides have been disclosed in International Patent Application No. PCT/US98/08212, Publication No. WO 98/49310.

### **Introduction**

The present invention is based upon the discovery that IL-17B or IL-17 can induce the proliferation and/or differentiation of retinal stem cells. IL-17B can be used to treat many ocular disorders in which retinal neurons have degenerated, such as macular degeneration and glaucoma. Age-related macular degeneration is the leading cause of blindness in the United States. Currently, there is no satisfactory treatment. In promoting the proliferation of retinal stem cells, one can administer IL-17B directly into the retina or by a gene therapy modality to stimulate the growth of endogenous stem cells. Secondly, retinal stem cells can be removed from the patient and IL-17B can

be used to stimulate the growth of retinal stem cells *in vitro*, and then transplant the stem cells back into the retina of the patient.

Those skilled in the art will recognize that the sequences disclosed in SEQ ID NOs: 1, and 2 represent a single allele of the human IL-17B. One can clone  
5 allelic variants of these sequences by probing cDNA or genomic libraries from different individuals according to standard procedures.

#### Modes of Administration

In general, pharmaceutical formulations will include an IL-17B protein  
10 in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington: *The Science and Practice of Pharmacy*,  
15 Gennaro, ed., (Mack Publishing Co., Easton, PA, 19th ed., 1995). In a culture medium in which retinal stem cells are growing, the IL-17B should be present at a concentration of at least 100 ng/ml. If the IL-17B is administered directly into the retina, the therapeutic doses will generally be in the range of 0.1 to 100 µg/kg of patient weight, with the exact dose determined by the clinician according to accepted standards  
20 determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years.

#### Nucleic Acid-based Therapeutic Treatment

25 IL-17B can be also administered to a retinal stem cell by means of gene therapy. In one embodiment, a gene encoding an IL-17B polypeptide is introduced *in vivo* in a viral vector. Such vectors include an attenuated or defective DNA virus, such as but not limited to herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adeno-associated virus (AAV), and the like. Defective viruses,  
30 which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes virus 1 (HSV1) vector [Kaplitt *et al.*, *Molec. Cell. Neurosci.* 2: 320-330  
35 (1991)], an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet *et al.*, *J. Clin. Invest.* 90 :626-630 (1992), and a defective adeno-associated

virus vector [Samulski *et al.*, *J. Virol.*, 61:3096-3101 (1987); Samulski *et al.* *J. Virol.*, 63:3822-3828 (1989)].

In another embodiment, the gene can be introduced into a retinal stem  
5 cell by means of a retroviral vector, *e.g.*, as described in Anderson *et al.*, U.S. Patent  
No. 5,399,346; Mann *et al.*, *Cell*, 33:153 (1983); Temin *et al.*, U.S. Patent No.  
4,650,764; Temin *et al.*, U.S. Patent No. 4,980,289; Markowitz *et al.*, *J. Virol.* 62:1120  
(1988); Temin *et al.*, U.S. Patent No. 5,124,263; International Patent Publication No.  
WO 95/07358, published March 16, 1995 by Dougherty *et al.* and Blood, 82:845  
10 (1993).

Alternatively, the vector can be introduced by lipofection *in vivo* using  
liposomes. Synthetic cationic lipids can be used to prepare liposomes for *in vivo*  
transfection of a gene encoding a marker [Felgner *et al.*, *Proc. Natl. Acad. Sci. USA*,  
84:7413-7417 (1987); see Mackey *et al.*, *Proc. Natl. Acad. Sci. USA*, 85:8027-8031  
15 (1988)]. The use of lipofection to introduce exogenous genes into specific organs *in*  
*vivo* has certain practical advantages. Molecular targeting of liposomes to specific cells  
represents one area of benefit. It is clear that directing transfection to particular cells  
represents one area of benefit. It is clear that directing transfection to particular cell  
types would be particularly advantageous in a tissue with cellular heterogeneity, such as  
20 the pancreas, liver, kidney, and brain. Lipids may be chemically coupled to other  
molecules for the purpose of targeting. Targeted peptides, *e.g.*, hormones or  
neurotransmitters, and proteins such as antibodies, or non-peptide molecules could be  
coupled to liposomes chemically.

It is possible to remove the retinal stem cells from the body and  
25 introduce the vector as a naked DNA plasmid and then re-implant the transformed cells  
into the body. Naked DNA vector for gene therapy can be introduced into the desired  
host cells by methods known in the art, *e.g.*, transfection, electroporation,  
microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate  
precipitation, use of a gene gun or use of a DNA vector transporter [see, *e.g.*, Wu *et al.*,  
30 *J. Biol. Chem.*, 267:963-967 (1992); Wu *et al.*, *J. Biol. Chem.*, 263:14621-14624  
(1988)].

Example 1  
Cloning of IL-17B

IL-17B was identified from expressed sequence tag (EST) 582069 (SEQ ID NO: 3) by its homology to Interleukin-17. The EST582069 cDNA clone was obtained from the IMAGE™ consortium Lawrence Livermore National Laboratory through Genome Systems, Inc. The cDNA was supplied as an agar stab containing *E. coli* transfected with the plasmid having the cDNA of interest and then streaked out on an LB 100 µg/ml ampicillin and 100 µg/ml methicillin plate. The cDNA insert in EST582069 was sequenced. The insert was determined to be 717 base pairs long with a 180 amino acid open reading frame and a 22 amino acid signal peptide.

Example 2  
Construction of IL-17B Expression Vectors

A 473 bp IL-17B PCR DNA fragment was generated with 1 µl of a dilution of the EST582069 plasmid prep of Example 1 and 20 picomoles (pm) of primer SEQ ID NO: 4 and 20 pm primer SEQ ID NO: 5. The digested reaction mixture was electrophoresed on a 1% TBE gel; the DNA band was excised with a razor blade and the DNA was extracted from the gel with the Qiaquick® Gel Extraction Kit (Qiagen). The excised DNA was subcloned into plasmid nfpzp9, which had been cut with *Bam* and *Xho*. Nfpzp9 is a mammalian cell expression vector comprising an expression cassette containing the mouse metallothionein-1 promoter, a sequence encoding the tissue plasminogen activator (TPA) leader, then multiple restriction sites. These were followed by the human growth hormone terminator, an *E. coli* origin of replication and a mammalian selectable marker expression unit containing the SV40 promoter, enhancer and origin of replication, a dihydrofolate reductase gene (DHFR) and the SV40 terminator.

IL-17B was purified by means of affinity chromatography using anti-IL-17B antibodies.

Example 3  
Cloning of Murine IL-17B

Mouse IL-17B was identified from an expressed sequence tag (EST)  
5 660242 (SEQ ID NO: 8). EST660242 cDNA clone was obtained from the IMAGE  
consortium Lawrence Livermore National Laboratory through Genome Systems, Inc.  
The cDNA was supplied as an agar stab containing E. coli transfected with the plasmid  
having the cDNA of interest and then streaked out on an LB 100 µg/ml ampicillin, 25  
µg/ml methicillin plate. The cDNA insert in EST660242 was sequenced. The insert was  
10 determined to be 785 base pairs with an open reading frame of 180 amino acids and a  
putative 20 amino acid signal peptide. The sequences are defined by SEQ ID NO: 7 and  
SEQ ID NO: 6.

Example 4  
Proliferation of Retinal Stem Cells in Culture

Retinal stem cells were obtained from the retina of E17-18 rat embryos  
and grown in culture. Preliminary results indicate that human recombinant IL-17B  
stimulates the growth of retinal stem cells. The cells spread out on the substrate within  
20 one day, and the IL-17B-treated cells appeared to proliferate more rapidly than the  
control cells. We verified that IL-17B stimulated the proliferation of these cells by  
using an antibody that recognizes a protein present in M-phase cells (phosphohistone3).  
We found many more cells labeled with phospho-histone3 antibody in the culture  
containing the IL-17B.

25

## CLAIMS

We claim:

1. A method for inducing the proliferation and/or differentiation of retinal stem cells comprising bringing the retinal stem cells into contact with interleukin-17B (IL-17B).
2. The method of claim 1 wherein the IL-17B polypeptide is selected from the group consisting of SEQ ID NOs: 2, 7, and 9-28.
3. The method of claim 1 wherein the retinal stem cells are grown in a culture medium.
4. The method of claim 3 wherein the retinal stem cells are implanted into the retina of a mammal after the stems cells have come into contact with IL-17B.
5. A method for inducing the proliferation and/or differentiation of retinal stem cells comprising administering IL-17B into the retina.



## SEQUENCE LISTING

<110> ZymoGenetics, Inc.  
University of Washington  
Emma E. Moore  
Thomas Reh

<120> Method for Proliferation of Retinal Stem  
Cells

<130> 01-13PC

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<151> 2001-03-26

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<400> 10
Gln Pro Arg Ala Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly
1      5      10      15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20      25      30
Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu
35      40      45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50      55      60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65      70      75      80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85      90      95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100     105     110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115     120     125
Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg
130     135     140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145     150     155     160

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<210> 11
<211> 160

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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 11

Gln	Pro	Arg	Ser	Pro	Lys	Ala	Lys	Arg	Lys	Gly	Gln	Gly	Arg	Pro	Gly
1			5						10					15	
Pro	Leu	Ala	Pro	Gly	Pro	His	Gln	Val	Pro	Leu	Asp	Leu	Val	Ser	Arg
			20					25					30		
Met	Lys	Pro	Tyr	Ala	Arg	Met	Glu	Glu	Tyr	Glu	Arg	Asn	Ile	Glu	Glu
		35					40					45			
Met	Val	Ala	Gln	Leu	Arg	Asn	Ser	Ser	Glu	Leu	Ala	Gln	Arg	Lys	Cys
		50				55					60				
Glu	Val	Asn	Leu	Gln	Leu	Trp	Met	Ser	Asn	Lys	Arg	Ser	Leu	Ser	Pro
65					70					75				80	
Trp	Gly	Tyr	Ser	Ile	Asn	His	Asp	Pro	Ser	Arg	Ile	Pro	Val	Asp	Leu
				85					90					95	
Pro	Glu	Ala	Arg	Cys	Leu	Cys	Leu	Gly	Cys	Val	Asn	Pro	Phe	Thr	Met
			100					105					110		
Gln	Glu	Asp	Arg	Ser	Met	Val	Ser	Val	Pro	Val	Phe	Ser	Gln	Val	Pro
		115					120					125			
Val	Arg	Arg	Arg	Leu	Cys	Pro	Pro	Pro	Pro	Arg	Thr	Gly	Pro	Cys	Arg
	130					135					140				
Gln	Arg	Ala	Val	Met	Glu	Thr	Ile	Ala	Val	Gly	Cys	Thr	Cys	Ile	Phe
145					150					155					160

&lt;210&gt; 12

&lt;211&gt; 160

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

Gln	Pro	Arg	Ser	Pro	Lys	Ser	Lys	Arg	Lys	Gly	Gln	Gly	Arg	Pro	Ala
1			5						10					15	
Pro	Leu	Ala	Pro	Gly	Pro	His	Gln	Val	Pro	Leu	Asp	Leu	Val	Ser	Arg
			20					25					30		
Met	Lys	Pro	Tyr	Ala	Arg	Met	Glu	Glu	Tyr	Glu	Arg	Asn	Ile	Glu	Glu
		35					40					45			
Met	Val	Ala	Gln	Leu	Arg	Asn	Ser	Ser	Glu	Leu	Ala	Gln	Arg	Lys	Cys
		50				55					60				
Glu	Val	Asn	Leu	Gln	Leu	Trp	Met	Ser	Asn	Lys	Arg	Ser	Leu	Ser	Pro
65					70					75				80	
Trp	Gly	Tyr	Ser	Ile	Asn	His	Asp	Pro	Ser	Arg	Ile	Pro	Val	Asp	Leu
				85					90					95	
Pro	Glu	Ala	Arg	Cys	Leu	Cys	Leu	Gly	Cys	Val	Asn	Pro	Phe	Thr	Met
			100					105					110		
Gln	Glu	Asp	Arg	Ser	Met	Val	Ser	Val	Pro	Val	Phe	Ser	Gln	Val	Pro
		115					120					125			
Val	Arg	Arg	Arg	Leu	Cys	Pro	Pro	Pro	Pro	Arg	Thr	Gly	Pro	Cys	Arg
	130					135					140				
Gln	Arg	Ala	Val	Met	Glu	Thr	Ile	Ala	Val	Gly	Cys	Thr	Cys	Ile	Phe
145					150					155					160

&lt;210&gt; 13

&lt;211&gt; 160

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

Gln	Pro	Arg	Ser	Pro	Lys	Ser	Lys	Arg	Lys	Gly	Gln	Gly	Arg	Pro	Gly
1			5						10					15	
Pro	Leu	Ala	Pro	Gly	Pro	His	Gln	Val	Pro	Leu	Asp	Leu	Val	Ala	Arg
			20					25					30		

Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 35 40 45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 50 55 60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 65 70 75 80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 85 90 95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
 100 105 110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
 115 120 125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
 130 135 140  
 Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155 160

<210> 14  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 14  
 Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly  
 1 5 10 15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg  
 20 25 30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 35 40 45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 50 55 60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 65 70 75 80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 85 90 95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
 100 105 110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
 115 120 125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
 130 135 140  
 Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155 160

<210> 15  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 15  
 Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly  
 1 5 10 15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg  
 20 25 30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 35 40 45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 50 55 60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 65 70 75 80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 85 90 95

Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
                   100                  105                  110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
                   115                  120                  125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
                   130                  135                  140  
 Gln Arg Leu Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
   145                  150                  155                  160

<210> 16  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 16  
 Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly  
   1                  5                  10                  15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg  
                   20                  25                  30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
                   35                  40                  45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
   50                  55                  60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
  65                  70                  75                  80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
                   85                  90                  95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
                   100                  105                  110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
                   115                  120                  125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
  130                  135                  140  
 Gln Arg Phe Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
  145                  150                  155                  160

<210> 17  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 17  
 Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly  
   1                  5                  10                  15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Gly Arg  
                   20                  25                  30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
                   35                  40                  45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
   50                  55                  60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
  65                  70                  75                  80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
                   85                  90                  95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
                   100                  105                  110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
                   115                  120                  125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
  130                  135                  140  
 Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
  145                  150                  155                  160



<210> 18  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 18  
 Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Ser  
 1 5 10 15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg  
 20 25 30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 35 40 45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 50 55 60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 65 70 75 80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 85 90 95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
 100 105 110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
 115 120 125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
 130 135 140  
 Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155 160

<210> 19  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 19  
 Gln Pro Arg Ser Pro Lys Val Lys Arg Lys Gly Gln Gly Arg Pro Gly  
 1 5 10 15  
 Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg  
 20 25 30  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 35 40 45  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 50 55 60  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 65 70 75 80  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 85 90 95  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
 100 105 110  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
 115 120 125  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg  
 130 135 140  
 Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155 160

<210> 20  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 20  
 Gln Pro Arg Val Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly

10

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1           5           10           15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
20           25           30
Met Lys Pro Tyr Ala Arg Met Glu Tyr Glu Arg Asn Ile Glu Glu
35           40           45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys
50           55           60
Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro
65           70           75           80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu
85           90           95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
100          105          110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
115          120          125
Val Arg Arg Arg Leu Cys Pro Pro Pro Arg Thr Gly Pro Cys Arg
130          135          140
Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145          150          155          160

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<210> 21
<211> 158
<212> PRT
<213> Homo sapiens

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```

<400> 21
Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu
1           5           10           15
Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys
20           25           30
Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val
35           40           45
Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val
50           55           60
Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly
65           70           75           80
Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu
85           90           95
Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu
100          105          110
Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg
115          120          125
Arg Arg Leu Cys Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg
130          135          140
Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145          150          155

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<210> 22
<211> 154
<212> PRT
<213> Homo sapiens

```

```

<400> 22
Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro
1           5           10           15
His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg
20           25           30
Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg
35           40           45
Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu
50           55           60
Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn

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11

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65          70          75          80
His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu
      85          90          95
Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met
      100        105        110
Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys
      115        120        125
Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu
      130        135        140
Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
145          150

```

<210> 23  
 <211> 151  
 <212> PRT  
 <213> Homo sapiens

```

<400> 23
Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His Gln Val
1      5      10      15
Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu
      20      25      30
Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser
      35      40      45
Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser
      50      55      60
Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro
65      70      75      80
Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly
      85      90      95
Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val
      100     105     110
Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro
      115     120     125
Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala
      130     135     140
Val Gly Cys Thr Cys Ile Phe
145          150

```

<210> 24  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

```

<400> 24
His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln Gly Arg Pro Ser
1      5      10      15
Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg
      20      25      30
Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Leu Gly Glu
      35      40      45
Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala Lys Lys Lys Cys
      50      55      60
Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg Ser Leu Ser Pro
65      70      75      80
Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Ala Asp Leu
      85      90      95
Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met
      100     105     110
Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro
      115     120     125
Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro Gly Pro Cys Arg

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12

130 135 140  
 Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155 160

<210> 25  
 <211> 158  
 <212> PRT  
 <213> Homo sapiens

<400> 25  
 Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln Gly Arg Pro Ser Pro Leu  
 1 5 10 15  
 Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Val Lys  
 20 25 30  
 Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Leu Gly Glu Met Val  
 35 40 45  
 Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala Lys Lys Lys Cys Glu Val  
 50 55 60  
 Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly  
 65 70 75 80  
 Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Ala Asp Leu Pro Glu  
 85 90 95  
 Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu  
 100 105 110  
 Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg  
 115 120 125  
 Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro Gly Pro Cys Arg Gln Arg  
 130 135 140  
 Val Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150 155

<210> 26  
 <211> 153  
 <212> PRT  
 <213> Homo sapiens

<400> 26  
 Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His  
 1 5 10 15  
 Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met  
 20 25 30  
 Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn  
 35 40 45  
 Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp  
 50 55 60  
 Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His  
 65 70 75 80  
 Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys  
 85 90 95  
 Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val  
 100 105 110  
 Ser Val Pro Val Phe Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro  
 115 120 125  
 Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr  
 130 135 140  
 Ile Ala Val Gly Cys Thr Cys Ile Phe  
 145 150

<210> 27  
 <211> 128  
 <212> PRT  
 <213> Homo sapiens

<400> 27  
 Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu  
 1 5 10 15  
 Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys  
 20 25 30  
 Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro  
 35 40 45  
 Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu  
 50 55 60  
 Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met  
 65 70 75 80  
 Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro  
 85 90 95  
 Val Arg Arg Arg Leu Cys Pro Pro Pro Arg Thr Gly Pro Cys Arg  
 100 105 110  
 Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe  
 115 120 125

<210> 28  
 <211> 157  
 <212> PRT  
 <213> Homo sapiens

<400> 28  
 Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln Gly Arg Pro Gly Pro Leu  
 1 5 10 15  
 Ala Pro Gly Pro His Gln Val Pro Leu Asp Leu Val Ser Arg Met Lys  
 20 25 30  
 Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg Asn Ile Glu Glu Met Val  
 35 40 45  
 Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val  
 50 55 60  
 Asn Leu Gln Leu Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly  
 65 70 75 80  
 Tyr Ser Ile Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu  
 85 90 95  
 Ala Arg Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu  
 100 105 110  
 Asp Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg  
 115 120 125  
 Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln Arg  
 130 135 140  
 Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile  
 145 150 155

